NOVEL REACTIONS VIA β-CARBOLINE INTERMEDIATES

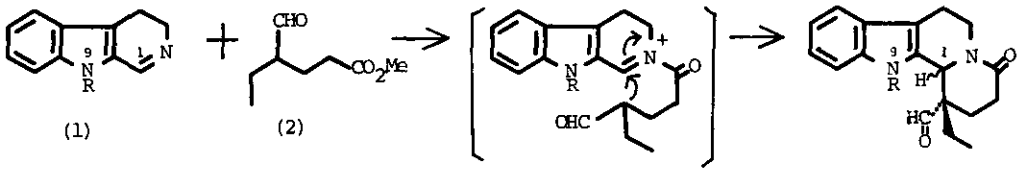
Seiichi Takano*, Kozo Shishido, Yoko Imamura, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract-------Novel reactions via some β-carboline intermediates have been described. Namely, the carboline(1a) gave the tetracyclic lactam(4a) when it was thermally condensed with the formyl ester(2), while its 9-methyl homologue(1b), on the same treatment, gave the 2-formylindole derivative(12). On the other hand, the carboline(13) yielded the tetracyclic lactam(16) when it was treated with butyryl chloride in the presence of triethylamine, whereas the carboline-acid chloride(18), prepared *in situ* from the amide-acid(17), took different course giving the 2-formylindole(23) on the same treatment.

During the course of our program toward the synthesis in the indole alkaloid field, we have encountered some interesting reactions involving the β-carboline intermediates.

In the first case, condensation of the carboline[1](1a) with methyl 3-formylhexanoate[2] at 150 °C using a sealed tube afforded the tetracyclic lactam(4) in separable diastereomeric forms as we have expected[3]. Of two diastereomers, the α-isomer[4](4, 1-(α)H, 20% yield, δ 9.91(1H, s), 5.18(1H, s), 0.85(3H, t, J=7 Hz) ppm, was readily differentiated from the β-isomer(4, 1-(β)H), 17% yield, δ 9.37(1H, s), 4.85(1H, s), 0.95(3H, t, J=7 Hz) ppm, as only the latter afforded the pentacyclic aminoacetal, δ 4.93(1H, s), 4.57(1H, br s) ppm, via intramolecular cyclization between the formyl group and the nitrogen at the 9-position when it was heated with ethanol in the presence of p-toluenesulfonic acid.

However, the 9-methyl homologue[5](1b) did not yield the expected tetracyclic homologue(4b) under the same thermal condensation and instead it afforded the 2-formylindole(12), δ 10.20(1H, s), 6.47(1H, br s), 4.10(3H, s) ppm, in 51% yield as an only isolable compound.

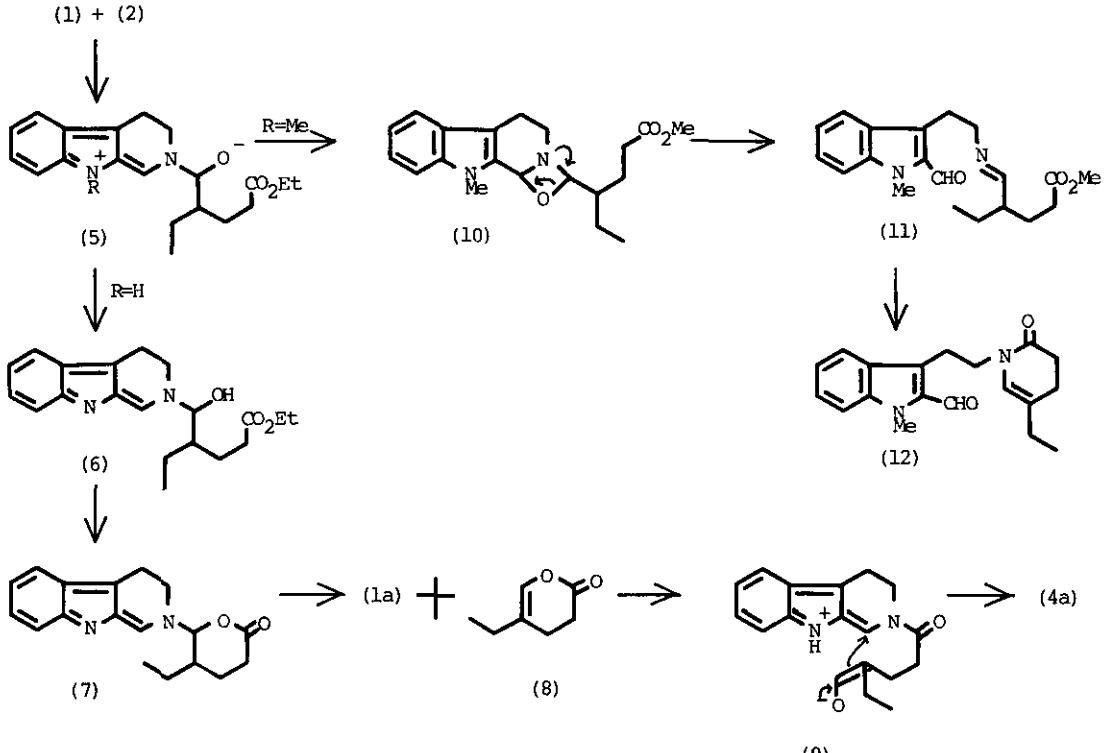


(1) (2) (3) (4)

a series: R=H, b series: R=Me

Scheme 1

The striking contrast between two carboline derivatives under the same conditions suggested us that the condensation occurred not in the way that we have initially presumed as in Scheme 1, but in the more complex way as in Scheme 2. Namely, the carbolines(1, a and b) attacked the dicarbonyl compound(2) initially at the more electrophilic formyl center giving rise to the transient betaine intermediates(5). Of these, the former(5a), capable of transferring the proton, yielded the tetracyclic lactam(4a) through a concurrent sequence of reactions, such as proton transfer(6), lactonization(7), elimination and recombination((1a)+(8)), and cyclization(9), while the latter(5b), incapable of the proton transfer, furnished the 2-formylindole(12) through concurrent oxazetidine formation(10), fragmentation(11), and cyclization(12).

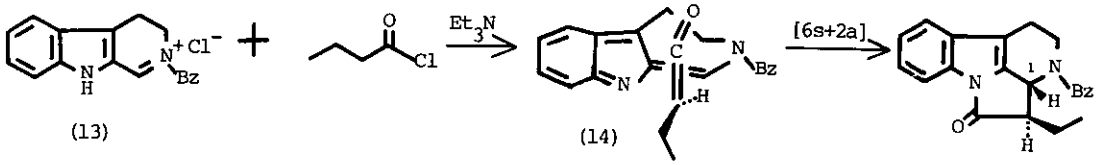


(1) + (2)

(5) (10) (11) (6) (12) (7) (1a) (8) (9) (4a)

Scheme 2

In the second case, the carboline[6](13) afforded the tetracyclic lactam(16), mp 85-87 °C, νmax 1740 cm^{-1}, δ 7.87(1H, m), 3.33(1H, d, J=13 Hz), 4.05(1H, d, J=13 Hz) ppm, in 58% yield on condensation with butyryl chloride in the presence of an excess amount of triethylamine in methylene chloride at 0 °C. The stereochemistry of the product(16) was deduced to be the trans configuration by means of ^{1}H-NMR spectroscopy using the dihedral angle calculation[7] based on the coupling constant of the proton at the 1-position(δ 3.71(J=6.0 Hz), φ=130°). The observed stereoselectivity indicated that the reaction proceeded through the [6s+2a]cycloaddition[8] between the enamine(14) and the ketene(15), both being generated from the corresponding progenitors by the action of triethylamine, as we have expected[8b].

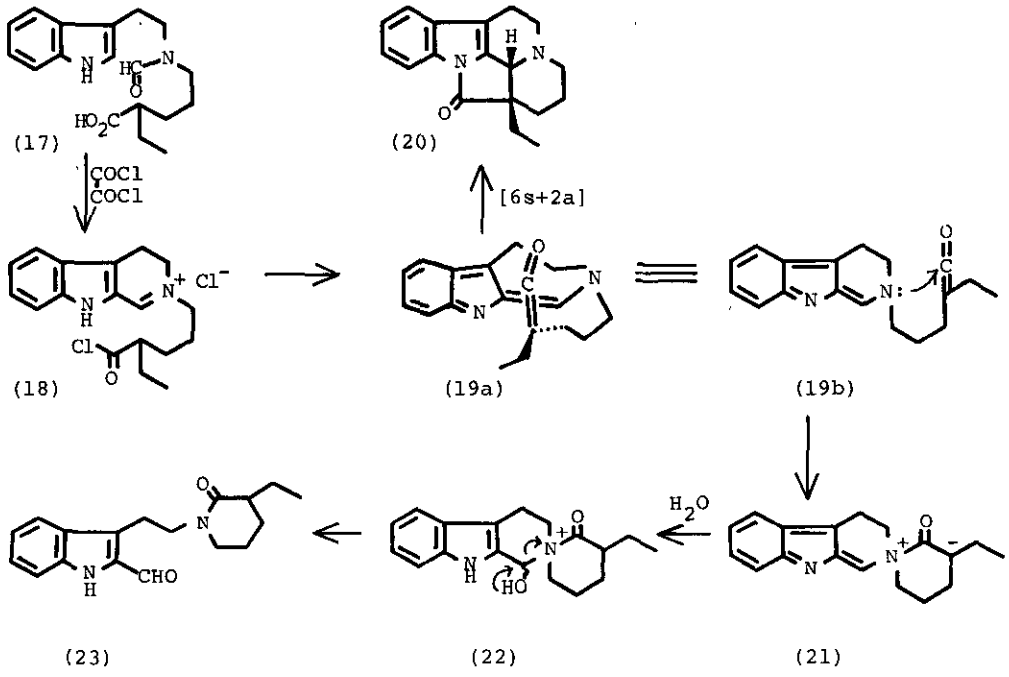


(13) (14) (15) (16)

Scheme 3

In order to initiate the same stereoselective [6s+2a]cycloaddition in intramolecular way, we prepared the carboline-acid chloride(18) from the amide-acid[9](17). Treatment of (17) with oxalyl chloride in methylene chloride at 0 °C afforded directly the desired compound[10](18) without difficulty through the concurrent acid chloride formation and Bischler-Napieralski type cyclization. We assumed that this carboline-acid chloride(18) should furnish the ketene-enamine(19), upon treatment with triethylamine, which would then undergo the intramolecular [6s+2a]cycloaddition yielding stereoselectively the pentacyclic lactam(20), a potential intermediate for the synthesis of the Vincamine-Eburnamine type indole alkaloids[11]. However, the product isolated after the same treatment as in the intermolecular reaction gave no expected one(20), but the 2-formylindole(23), mp 135-137 °C, νmax 1660, 1620 cm^{-1}, δ 9.93(1H, s), 9.63(1H, br s), 2.93(2H, br t, J=4 Hz) ppm, in 27% yield. Exclusive formation of (23) may be explained in terms of stereochemical difficulty in the requisite conformation(19a) for the intramolecular cycloaddition to yield the pentacyclic lactam(20). Under these conditions the alternative less crowded configuration(19b) favorable for the intramolecular acylation would have prevailed to give the betaine(21) which then would have collapsed to yield the

aldehyde(23) via (22) on agueous work-up.



Scheme 4

REFERENCES AND NOTES

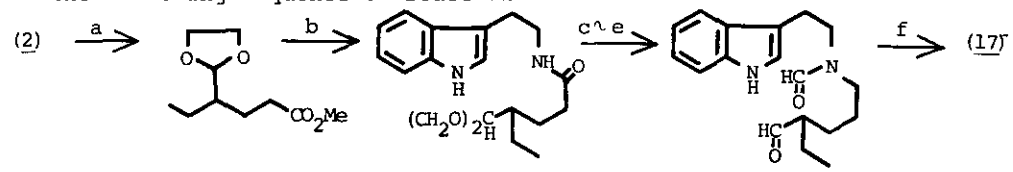
1. (a) N. Whittaker, J. Chem. Soc. C, 1969, 85. (b) D.D. O'Rell, F.G.H. Lee, and V. Boekelheide, J. Am. Chem. Soc., 1972, 94, 3205.
2. G. Stork, A. Brizzolara, H.K. Landesman, J. Szmuszkovicz, and R. Terell, J. Am. Chem. Soc., 1963, 85, 207.
3. Oppolzer reported the condensation of the carboline(1a) and 4-bromo-2-ethylpentanal(2:-CO_2Me=-CH_2Br) to form the tetracyclic amine(4:lactam-C=O=-CH_2) in poor yield(10%), though the yield was greatly improved by using the silyl ether of the aldehyde: W. Oppolzer, H. Hauth, P. Pfäffli, and R. Wenger, Helv. Chim. Acta., 1977, 60, 1801.
4. Satisfactory spectral(IR, ^{1}H-NMR, MS) and analytical(combustion and/or high resolution MS) data were obtained for all new compounds isolated. All ^{1}H-NMR spectra were recorded in deuteriochloroform solutions.
5. This compound was prepared from 1-methyltryptamine as the preparation of (1a).
6. This compound was prepared from (1a) on treatment with benzylchloride in

methylene chloride at room temperature.

7. Cf. L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd Ed., Pergamon Press, Oxford, 1969, p. 280.

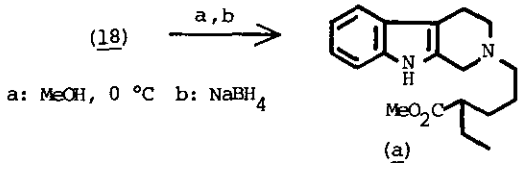
8. (a) Cf. I. Fleming, "Frontier Orbitals ans Organic Chemical Reactions", John Wiley & Sons, London, 1976, p. 143. (b) Cf. T. Kobayashi, S. Kajigaeshi, and S. Kanemasa, Heterocycles, 1976, 4, 1281.

9. This compound was prepared from the formyl ester(2) and tryptamine as shown in the following sequence of reactions:



a: $\subset^{OH}_{OH}$, p-TsOH b: tryptamine, Δ c: $LiAlH_4$ in THF d: HCOOEt, Δ e: dil.H_2SO_4 f: Ag_2O

10. Formation of (18) was confirmed by converting it into the tetrahydrocarboline derivative(a) by reduction with sodium borohydride after a brief treatment with anhydrous methanol.



a: MeOH, 0 °C b: $NaBH_4$

11. Cf. M. Hesse, "Indolalkaloids in Tabellen", Springer Verlag, Berlin, 1964 and 1968.

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